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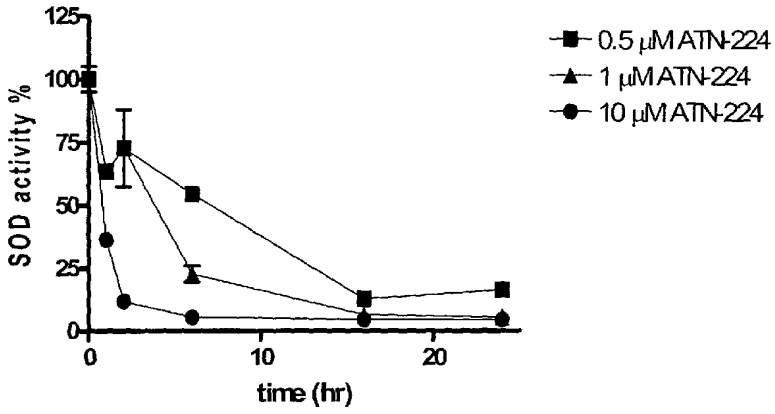
(54) Title: INHIBITION OF SUPEROXIDE DISMUTASE BY TETRATHIOMOLYBDATE: IDENTIFICATION OF NEW ANTI-ANGIOGENIC AND ANTITUMOR AGENTS



(57) Abstract: Though copper is elevated in the tumor tissue and plasma of patients with various malignancies, the molecular targets for copper binding agents in angiogenesis and tumor progression remain poorly understood. It is disclosed that one anti-angiogenic target for the copper binding agent tetrathiomolybdate is intracellular CuZn-superoxide dismutase (SOD1). A second generation tetrathiomolybdate analog, ATN-224, inhibits endothelial cell (EC) proliferation in vitro, binds to SOD1 and inhibits its activity without displacing bound copper. ATN-224 can accumulate in ECs and inhibit CuZnSOD activity with an IC_{50} similar to the IC_{50} for EC proliferation, resulting in increased generation of intracellular reactive oxygen species. Inhibition of EC proliferation by ATN-224 in vitro is substantially reversed by a synthetic porphyrin SOD mimetic. Similar results were observed in vivo, where inhibition of angiogenesis by ATN-224 in a Matrigel plug model was also reversed by MnTBAP. Thus, a distinct molecular target for copper depletion therapy has been identified and SOD1 is now validated as a target for anti-angiogenesis. Methods for screening, or designing, such SOD1 inhibitors for use as angiogenesis inhibitors and anti-cancer agents are disclosed.

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